REMARKS

Claims 1-24 are pending. Claims 1-10, 12-15 and 20-23 have been withdrawn.

Rejections Under 35 USC § 103

The Declaration under 37 C.F.R § 1.132 of Dr. Lanfranco Callegaro is submitted herewith in support of the arguments presented in the response of June 23, 2006. These arguments are summarized below, providing specific reference to Dr. Callegaro's statements.

Applicants do not believe that any further fees are due. If, however, some additional fees are due, especially extension of time fees, the Commissioner is authorized to charge Deposit Account No. 02-2448.

Della Valle in view of Malson

The Examiner has rejected claims 11, 16, 19 and 24 as obvious over Della Valle et al (EP 341745) in view of Malson et al (US 5,783,691). The Examiner contends that Della Valle teaches autocrosslinked HA with a 5% crosslinked product exemplified and the use of this product in a variety of forms. She states that the reference further states that the articles prepared using the HA products are "similar to those already known and commercially available or described in the literature." She acknowledges that the reference is silent regarding the prevention of surgical adhesions.

Turning to the Malson reference, the Examiner contends that it teaches that HA and crosslinked HA derivatives are known generally to be useful in medical applications such as prevention of post-operative adhesions. She also states that the reference teaches that the Malson

product is superior to other known crosslinked HAs because it introduces fewer "alien" products that may result in immunological or inflammatory reactions.

The Examiner concludes that a skilled artisan would use the Della Valle crosslinked HA products for the prevention of post-surgical adhesions and would reasonably expect success because Malson had taught that HA and crosslinked HA derivates are known to have this utility. Applicants respectfully traverse.

The Examiner has stated that the Malson reference is drawn specifically to HA that is crosslinked through phosphate ester linkages and that is useful for the applications know for HA per se and other crosslinked HA derivatives, such as preventing post-surgical adhesions. She also states that the Malson product is superior because it introduces fewer "alien" products that may result in immunological or inflammatory reactions.

But this is not the case. As discussed by Dr. Callegaro in the accompanying Declaration, the crosslinked HA of the Malson reference is an HA gel derivative which is produced by means of reacting the HA with a phosphorus-containing reagent as a crosslinking reagent, which may be phosphorus pentachloride, phosphorus oxychloride or phosphorus pentoxide. As Dr. Callegaro points out, such reagents are, however, highly toxic, as reported in the Merk Index (see attached) where it is clearly stated that they are corrosive on both the mucosa and skin. Moreover, in the attached abstract (Segall et al. (2003) Chem Res Toxicol 16: 350-356) these substances are used to produce pesticides because they inhibit vital enzymes such as acetylcholinesterase, even at very low concentrations, e.g. those measured in μM amounts.

In the accompanying Declaration, Dr. Callegaro states that Example 2 of the Malson reference allows calculation of the quantity of phosphorus oxychloride used to crosslink 300 mg

of HA. Here, 400 µl of phosphorus oxychloride is used to crosslink 300 mg of HA. Knowing that $POCl_3$ has a density of d = 1.645 and Mw = 153.33 (Merk Index), since d = m/v, the following calculation can be made: 1.645 = grams/0.4 ml (i.e .400 µl). Thus, 400 µl corresponds to 0.658 grams. Since the Mw is know, the number of moles contained within 400 µl of $POCl_3$ can be calculated as 0.658/1.53.33 = 0.0043 moles. This allows calculation of the molarity of the solution prepared in Example 2 as follows: 0.0043 moles/15 X 1000 = 0.28M. This value of 0.28 M is very high, indeed the attached abstract indicates that concentrations measured in µM are strong enough to be poisonous.

Dr. Callegaro indicates that such an enormous quantity of toxic substance(s) could likely **not** be completely eliminated without trace amounts remaining present. This is especially so since Example 2 calculates the phosphorus content of the gel as 0.1%, but the body of the patent states that it is sometimes as high as 1% (see column 4, line 2), which suggests that the values might be influenced by residual crosslinking agent that has not been entirely eliminated. Dr. Callegaron notes that no biological data is presented in the Malson reference, only synthesis. He indicates that it is obvious that any derivative that has the potential to release highly poisonous substances, or degradation products that could react in the physiological environment to produce poisonous substances, could never be used in surgery, let alone to prevent the formation of adhesions.

The Examiner also states that the Malson reference has fewer "alien" products than other known crosslinked HAs. While this may be true, Dr. Callegaro points out that the Malson HA derivatized gel contains phosphorus bridges that crosslink the HA chains, but that these phosphorus bridges are substances that are foreign to the HA molecule per se. On the other hand,

he notes that the crosslinked HA gel of the instant invention does not contain any foreign molecules and degrades without producing any potentially dangerous or reactively dangerous products. Even if, as the Examiner suggests, the Malson products have "fewer" alien products than other known products, the products used in the present invention degrade **without** producing **any** alien products. This presents an unexpectedly improved result over the Malson products.

Dr. Callegaro notes that a direct comparison of the Malson product and the HA derivative gel of the instant invention is not practical since *in vivo* tests using live animal models would be necessary and because it is extremely difficult to obtain approval for tests that are known to inflict pain and suffering on animals. Because of the high potential for toxicity from use of the Malson product in an animal model, it would be difficult to ethically conduct such comparative test and/or to obtain permission to do so.

The Examiner states that Malson teaches that HA and crosslinked HA derivatives are known **generally** to be useful in medical applications. But this does not mean that all HA derivatives and crosslinked derivatives are useful for each and every purpose. One skilled in the art understands that one cannot simply switch various HA derivative products and achieve the same result. Consequently, it would not be obvious to use the Della Valle materials for prevention of post-surgical adhesions. The Examiner may think that it is obvious to try, but this is not the proper standard.

In view of the above, applicants respectfully request reconsideration and removal of the rejection.

Della Valle in view of Malson and Matsuda

The Examiner has rejected claims 11, 16, 19 and 20 as obvious over Della Valle in combination with Malson and Matsuda (US 5,462,976). The Della Valle and Malson references are discussed above. The Examiner acknowledges that these references do not teach the range of forms listed in claim 19.

With respect to Matsuda, the Examiner contends that this reference also teaches that glycosaminoglycans, such as HA, are useful for the prevention of surgical adhesions as well as teaching that these crosslinked biopolymers may be prepared in a variety of forms.

The Examiner contends that it would have been obvious to the skilled artisan to prepare the Della Valle crosslinked HA material in any form known to be used for surgical applications with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above and supported by Dr. Callegaro's Declaration, the skilled artisan realizes that **not** all HA derivatives and crosslinked derivatives are useful for each and every purpose. One skilled in the art understands that one cannot simply switch various HA derivative products and achieve the same result. Consequently, even considering the combined teachings with Matsuda, it would not be obvious to use the Della Valle materials for prevention of post-surgical adhesions. While the Examiner may think that it is obvious to try, again this is not the proper standard.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Della Valle in view of Malson and Leshchiner

The Examiner has rejected claims 11, 16, 19 and 24 as obvious over Della Valle in combination with Malson and Leshchiner (US 5,399,351). The Della Valle and Malson references are discussed above. The Examiner acknowledges that these references do not teach any specific type of surgery.

Regarding Leshchiner, the Examiner contends the reference teaches that viscoelastic gels comprising crosslinked biopolymers, such as HA derivatives, have utility for prevention of post-operative adhesions.

The Examiner contends that it would have been obvious to the skilled artisan to prepare the Della Valle crosslinked HA material in any form known to be used for surgical applications with a reasonable expectation of success. Applicants respectfully traverse.

As discussed above and as evidenced by Dr. Callegaro's Declaration, the skilled artisan realizes that **not** all HA derivatives and crosslinked derivatives are useful for each and every purpose. One skilled in the art understands that one cannot simply switch various HA derivative products and achieve the same result. Consequently, even considering the combined teachings with Matsuda, it would not be obvious to use the Della Valle materials for prevention of post-surgical adhesions. While the Examiner may think that it is obvious to try, again, this is not the proper standard.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Applicants respectfully submit that all claims remaining in the case are drawn to novel, non-obvious patentable subject matter and request early allowance of the pending claims.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman (Reg. No. 47,604) in Costa Mesa, CA at telephone number 714-708-8555 to conduct an Interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

Dated: July 19, 2006

Respectfully submitted,

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ATTACHMENTS: DECLARATION UNDER 37 C.F.R. § 1.132